Reduced bone density at completion of chemotherapy for a malignancy

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Abstract

***Objectives*—Osteoporosis and pathological fractures occur occasionally in children with malignancies. This study was performed to determine the degree of osteopenia in children with a malignancy at completion of chemotherapy.**

***Methods*—Lumbar spine (L2–L4) bone mineral density (BMD; g/cm^2) and femoral neck BMD were measured by dual energy *x* ray absorptiometry in 22 children with acute lymphoblastic leukaemia (ALL), and in 26 children with other malignancies. Apparent volumetric density was calculated to minimise the effect of bone size on BMD. Results were compared with those of 113 healthy controls and expressed as age and sex standardised mean Z scores.**

***Results*—Patients with ALL had significantly reduced lumbar volumetric (−0.77) and femoral areal and volumetric BMDs (−1.02 and −0.98, respectively). In patients with other malignancies, femoral areal and apparent volumetric BMDs were significantly decreased (−0.70 and −0.78, respectively).**

***Conclusions*—The results demonstrate that children with a malignancy are at risk of developing osteopenia. A follow up of BMD after the completion of chemotherapy should facilitate the identification of patients who might be left with impaired development of peak bone mass, and who require specific interventions to prevent any further decrease in their skeletal mass and to preserve their BMD.**

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Keywords: bone mineral density; malignancy; osteopenia

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Developments in diagnostic and therapeutic methods have led to increased survival rates in children with malignancies. Around two thirds of these patients reach adulthood. Some of the side effects of cancer treatments are well recognised, and include growth retardation, cardiomyopathy, and effects on fertility. Skeletal manifestations, such as osteoporosis and fractures of long bones and spine, have also been described in children with malignancies.[1–11] However, little is known about bone mineralisation in these children.

In childhood acute lymphoblastic leukaemia (ALL), which is the most common malignancy occurring in children, skeletal changes are frequently found at the time of diagnosis. They include metaphyseal lines, periosteal reaction, osteolysis, sclerosis, osteoporosis, and occasionally pathological fractures. These changes have been attributed to the disease process and to the alterations in mineral homeostasis and bone mass.[4] Some forms of antineoplastic treatments, such as corticosteroids, methotrexate, and radiotherapy, are thought to be harmful to the development of bone mass and density.[2–13] Impaired accumulation of skeletal mass during childhood and adolescence might predispose these patients to osteoporosis and pathological fractures later in adulthood.

The purpose of our study was to determine the degree of osteopenia in children treated for malignancy at the time of completion of chemotherapy.

Patients and methods

PATIENTS

Our study series comprised 48 of the 69 white patients (23 boys, 25 girls) who completed their treatment for a childhood malignancy (22 cases of ALL, 26 other malignancies) in the Kuopio University Hospital between January 1995 and September 1997 (table 1). The patients were studied at the time of cessation of chemotherapy. None of the patients had a condition known or suspected to affect bone metabolism before diagnosis (a growth affecting chronic disease, bone disease, systemic corticosteroid treatment during the six months before diagnosis, history of radiotherapy, mental retardation, or physical disability). Twenty one of the 69 patients were not included in the study for the following reasons: 11 (one ALL) did not comply adequately with the study, eight (one ALL) refused, and two ALL patients had Down's syndrome. The study protocol was approved by the institutional ethics committee, Kuopio University Hospital, and written informed consent was obtained from every parent and appropriately aged patient.

Table 1 Clinical data of the study population

		Radiotherapy		
Disease	*Boys/ girls (n)*	*n*	*Dose (Gy)*	*Site*
ALL	10/12	2	18.0	Cranial
AML	1/2	–		
Lymphoma	5/5	–		
Medulloblastoma	0/1	1	78.6	Brain, spinal
Nephroblastoma	1/1	1	32.4	Tumour site
		1	10.8	Tumour site
Osteosarcoma	2/2	–		
Pinealoblastoma	0/1	1	82.2	Brain, spinal
PNET inguinalis	1/0	1	56.0	Inguinal region
Rhabdomyosarcoma	2/1	1	48.8	Iliacal, para-aortal regions
		1	50.4	Thoracal XII—sacral I
		1	48.0	Auricular regions
Teratoma malignum	0/1	–		

ALL, acute lymphblastic leukaemia; AML, acute myeloblastic leukaemia; PNET, primitive neuroectodermal tumour; Gy, grey.

Table 2 Clinical characteristics and treatment data of the study population (n = 48)

	Acute lymphoblastic leukaemia (n = 22)	*Other malignancy (n = 26)*	*Boys (n = 23)*	*Girls (n = 25)*
Age at diagnosis (years)	7.1 (1.5 to 14.8)	10.0 (3.4 to 16.9)	9.5 (1.5 to 16.9)	7.3 (1.8 to 14.5)
Age at study (years)	9.3 (3.6 to 16.9)	11.2 (4.4 to 17.7)	11.1 (3.6 to 17.8)	9.3 (3.8 to 16.2)
Bone age (years)	9.3 (4.0 to 18.2)	8.0 (3.5 to 18.2)	10.0 (4.4 to 18.2)	8.6 (3.5 to 16.0)
Body mass index (kg/m^2)	18.3 (13.9 to 27.3)	17.2 (12.6 to 27.5)	19.1 (13.2 to 27.3)	17.4 (12.6 to 27.5)
Relative height (SDS)	0.2 (−1.2 to 3.4)	−0.4 (−3.0 to 3.2)	−0.2 (−2.4 to 3.2)	0.2 (−3.0 to 3.4)
Duration of treatment (years)	2.0 (1.8 to 2.5)	0.6 (0.3 to 2.0)‡	1.3 (0.3 to 2.5)	1.3 (0.3 to 2.5)
Days of hospitalisation	139.5 (89.0 to 210.0)	93.0 (20.0 to 206.0)*	119.0 (20.0 to 195.0)	119.0 (21.0 to 210.0)
Weeks on corticosteroids	11.0 (9.0 to 12.0)	7.0 (2.0 to 18.0)‡	6.3 (2.0 to 12.0)	7.5 (4.0 to 18.0)
Doses				
Corticosteroids	5.4 (3.8 to 9.0) (n = 22)	2.4 (0.2 to 5.0)‡ (n = 11)	5.3 (0.6 to 5.4) (n = 15)	4.0 (0.2 to 9.0) (n = 18)
Cyclophosphamide	3.0 (3.0 to 30.0) (n = 17)	4.0 (0.04 to 82.0) (n = 15)	3.0 (0.1 to 30.0) (n = 16)	3.6 (0.04 to 82.0) (n = 16)
Cytarabine	1.8 (0.08 to 396.0) (n = 18)	1.8 (0.6 to 62.1)† (n = 10)	1.8 (1.0 to 40.3) (n = 13)	1.8 (0.08 to 396.0) (n = 15)
Doxorubicin	0.1 (0.1 to 0.3) (n = 22)	0.2 (0.08 to 0.4)* (n = 23)	0.2 (0.08 to 0.4) (n = 23)	0.2 (0.1 to 0.3) (n = 22)
Methotrexate	45.0 (6.0 to 45.0) (n = 22)	20.0 (3.0 to 108.0)‡ (n = 11)	45.0 (3.0 to 108.0) (n = 16)	40.0 (3.0 to 48.0) (n = 17)
Vincristine	28.0 (20.0 to 33.0) (n = 22)	14.8 (1.4 to 48.0)† (n = 14)	24.0 (1.4 to 46.0) (n = 17)	28.0 (8.4 to 48.0) (n = 19)

Values are median (range).
Chemotherapeutic agents as intravenous cumulative doses (g/m^2; vincristine, mg/m^2); corticosteroids as oral equivalent doses of prednisolone (g/m^2). *$p \leq 0.01$; †$p < 0.001$; ‡$p < 0.0001$; all compared with acute lymphoblastic leukaemia.

The median (range) age at diagnosis was 8.4 (1.5–16.9) years and at completion of chemotherapy 10.2 (3.6–17.8) years. The median (range) duration of chemotherapy was 1.3 (0.3–2.5) years (table 2). Data on pubertal development were available for 43 patients of whom 26 (11 boys, 15 girls) were prepubertal and 17 (eight boys, nine girls) were pubertal. None of the patients in the study group had been diagnosed to have growth hormone deficiency or were treated with growth hormone.

The ALL patients were treated according to the protocols of the Nordic Society of Pediatric Hematology and Oncology (NOPHO) based on the three risk groups of ALL: standard risk (two boys, three girls), intermediate risk (eight boys, five girls), and high risk (four girls).[14 15] The patients with a malignancy other than ALL were treated according to the international cancer protocols consisting of various multiagent chemotherapy regimens.[16–22] Table 2 presents data on the cumulative doses of antineoplastic agents used in both ALL and other malignancy groups (oral corticosteroids as equivalent doses of prednisolone, intravenous cyclophosphamide, cytarabine, doxorubicin, methotrexate, and vincristine). The duration of oral corticosteroid treatment was determined (table 2). Four patients with osteosarcomas had gone through a skeletal operation with prosthesis: three right femoral, one left tibial.

BONE MINERAL DENSITY

Areal bone mineral density (BMD; g/cm^2) of the lumbar spine (L2–L4) and left femoral neck was measured by dual energy *x* ray absorptiometry (Lunar DPX; Lunar Radiation Corporation, Madison, Wisconsin, USA). Because of device based soft tissue requirements, femoral BMD was measured only for children above 7 years of age. The coefficient of variation for the spine is 0.8% and for the femoral neck 2.3%.[23] To minimise the effect of bone size on BMD values, bone apparent volumetric mineral density (BMDvol; g/cm^3) was calculated from the areal BMD values: lumbar BMDvol = BMD (g/cm^2) × (4/(π × width of measurement area in lumbar spine)); femoral BMDvol = BMD (g/cm^2) × (4/π) × (height of measurement area/measurement area of femoral neck).[23] The results were compared with those of 113 healthy Finnish controls (55 boys, 58 girls; age 3.5–18.9 years) and expressed as age and sex standardised Z scores (mean; 95% confidence intervals (CI)).[23 24]

HORMONAL STATUS AND EVALUATION OF BONE AGE

Standard methods were used for the evaluation of serum hormonal status. Free thyroxine (n = 44) and thyrotropin (n = 45) were determined to exclude hypothyroidism. Luteinising hormone (n = 22), testosterone in boys (n = 11), and oestradiol in girls (n = 9) were determined for patients above 10 years of age

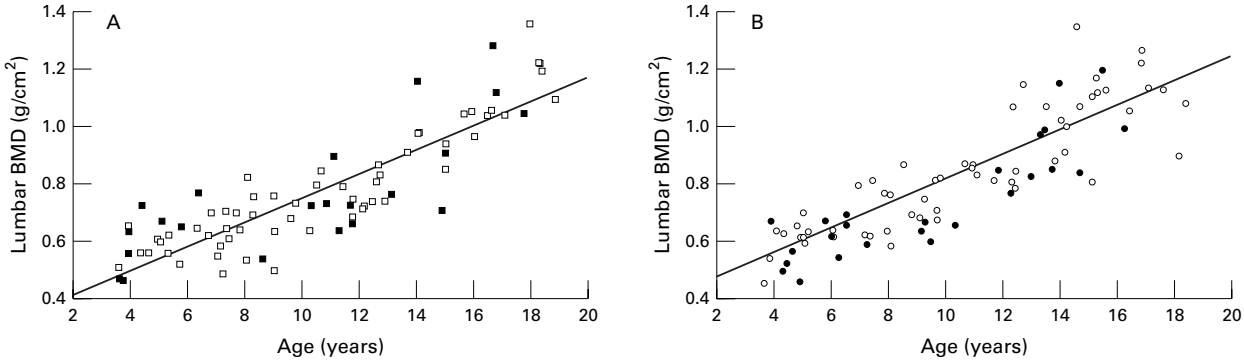

Figure 1 (A) The areal lumbar (L2–L4) BMD values (g/cm^2) in relation to age at the time of the study in the 22 male patients (closed squares). The regression line of the lumbar BMD values (g/cm^2) of the male controls (open squares) is shown. (B) The areal lumbar (L2–L4) BMD values (g/cm^2) in relation to age at the time of our study in the 25 female patients (closed circles). The regression line of the lumbar BMD values (g/cm^2) of the female controls (closed circles) is shown.

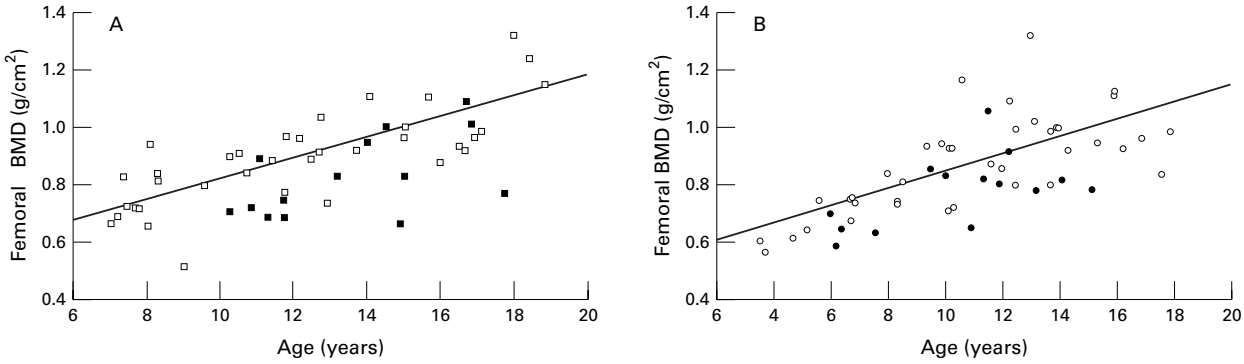

Figure 2 (A) The areal femoral neck bone BMD values (g/cm²) in relation to age at the time of our study in the 14 male patients (closed squares). The regression line of the femoral BMD values (g/cm²) of the male controls (open squares) is shown. (B) The areal femoral neck BMD values (g/cm²) in relation to age at the time of our study in the 14 female patients (closed circles). The regression line of the femoral BMD values (g/cm²) of the female controls (open circles) is shown.

(n = 25 (14 boys, 11 girls)) to exclude hypogonadism. Intact parathyroid hormone (n = 46) was analysed to exclude hyperparathyroidism. Laboratory specific, age and sex matched reference data were used in the assessment of serum hormonal variables.

Bone age at the time of our study was determined for 40 patients by one of the authors (JK) using a Tanner-Whitehouse (RUS) method.[25]

STATISTICS

Statistical analyses were carried out with the SPSS for Windows (6.0.1) statistical program. Because of the heterogeneity of the treatment protocols, two groups were formed for the statistical analyses: those with ALL and those with other malignancies. To facilitate the comparison of data, BMD values were converted to Z scores: the age and sex specific mean BMD value of the control group was subtracted from each patient's BMD value, and then divided by the corresponding age and sex specific standard deviation. A non-parametric one sample test (Wilcoxon) was used to compare the BMD Z scores with a constant of the controls. BMD, relative height (in standard deviation score (SDS) units), and BMI values, age at diagnosis, age at completion of treatment, bone age, and duration of treatment were compared between the patient groups by means of the Mann-Whitney U test, with p values < 0.05 considered significant. Partial correlation coefficients adjusted for age were calculated to correlate BMD Z scores with durations of corticosteroid and overall treatments (rank corrected), BMI, relative height, and days of hospitalisation. Non-parametric correlation coefficients were calculated to correlate age at diagnosis, age at study, and bone age with the BMD Z scores. A simultaneous regression analysis was used to analyse the independent correlations of the cumulative doses of chemotherapy agents with the BMD Z scores.

Results

Table 2 gives median BMI, relative height, and bone age values. BMI and relative height values were within the normal range for the age and sex matched controls.[23] No significant difference was found between the chronological age and bone age at the time of our study. In patients with ALL, duration of hospitalisation, corticosteroid treatment, and overall chemotherapy were significantly longer in comparison with the patients with other malignancies. The cumulative doses of oral corticosteroids and intravenous methotrexate were significantly higher in ALL patients than in other malignancies (table 2).

Figures 1 and 2 show the areal lumbar and femoral BMD values in relation to age. Table 3 gives the mean areal and apparent volumetric BMD values.

In patients with ALL, lumbar volumetric BMD (Z scores mean, −0.77; 95% CI, −1.30 to −0.23; p = 0.01), femoral areal BMD (Z scores mean, −1.02; 95% CI, −1.52 to −0.53; $p < 0.01$), and femoral volumetric BMD values (Z scores mean, −0.98; 95% CI, −1.64 to −0.32; $p < 0.01$) were significantly decreased compared with the healthy controls. In patients with other malignancies, femoral areal BMD (Z scores mean, −0.70; 95% CI, −1.19 to −0.21; p = 0.02) and apparent volumetric BMD values (Z scores mean, −0.78; 95% CI,

Table 3 Bone mineral density data of the study population (n = 48)

	Acute lymphoblastic leukaemia (n = 22)	*Other malignancy (n = 26)*	*Boys (n = 23)*	*Girls (n = 25)*
Mean (SD) absolute BMD				
Lumbar BMD (g/cm²)	0.72 (0.19) (n = 22)	0.79 (0.22) (n = 25)	0.77 (0.22) (n = 22)	0.74 (0.20) (n = 25)
Lumbar BMDvol (g/cm³)	0.27 (0.041) (n = 22)	0.30 (0.044) (n = 25)	0.28 (0.041) (n = 22)	0.29 (0.047) (n = 25)
Femoral BMD (g/cm²)	0.77 (0.14) (n = 12)	0.83 (0.13) (n = 16)	0.83 (0.14) (n = 14)	0.78 (0.13) (n = 14)
Femoral BMDvol (g/cm³)	0.35 (0.041) (n = 12)	0.36 (0.050) (n = 16)	0.35 (0.051) (n = 14)	0.36 (0.041) (n = 14)
Mean Z scores (95% CI)				
Lumbar BMD	−0.36 (−0.99 to 0.27)	−0.08 (−0.62 to 0.46)	0.13 (−0.62 to 0.89)	−0.52 (−0.88 to −0.15)*
Lumbar BMDvol	−0.77 (−1.30 to −0.23)*	−0.04 (−0.58 to 0.49)	−0.21 (−0.92 to 0.51)	−0.54 (−0.92 to −0.16)*
Femoral BMD	−1.02 (−1.52 to −0.53)*	−0.70 (−1.19 to −0.21)†	−0.89 (−1.48 to −0.30)*	−0.79 (−1.21 to −0.37)*
Femoral BMDvol	−0.98 (−1.64 to −0.32)*	−0.78 (−1.38 to −0.19)*	−0.91 (−1.62 to −0.21)*	−0.83 (−1.36 to −0.29)*

*$p \leq 0.01$; †p = 0.02; both compared with controls.

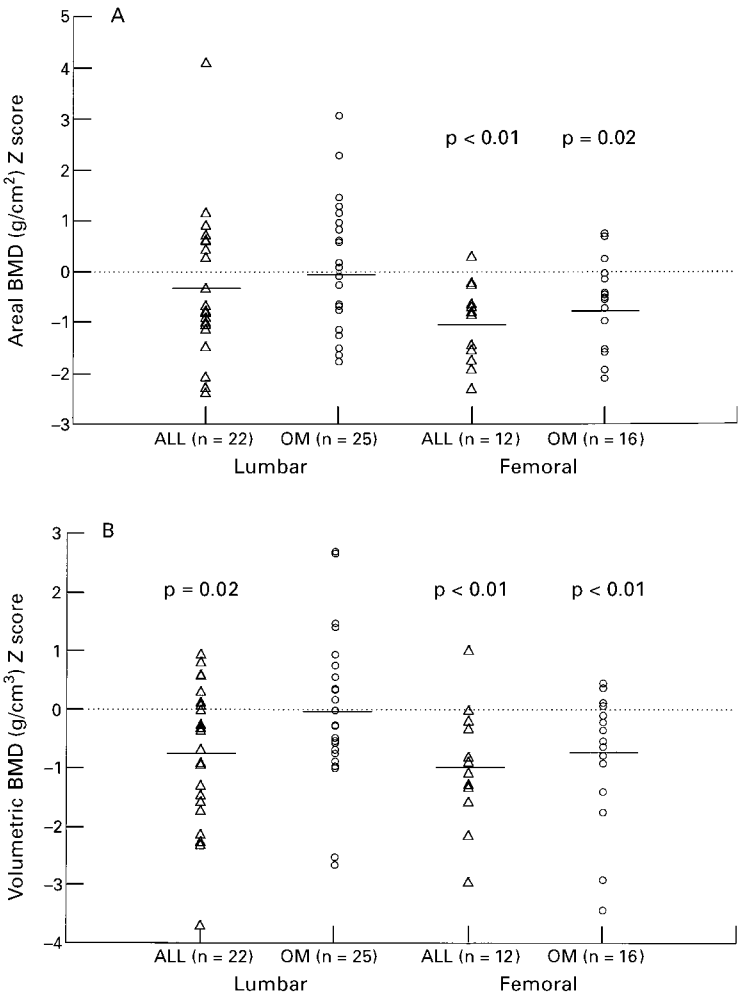

Figure 3 (A) The areal lumbar (L2–L4) and femoral BMD values (g/cm²) as Z scores (SDS) in ALL (triangles) and other malignancy (OM, circles) patients at completion of chemotherapy. p values as compared with controls; horizontal lines are mean BMD values. (B) The apparent volumetric lumbar (L2–L4) and femoral BMD values (g/cm³) as Z scores (SDS) in ALL (triangles) and other malignancy (OM; circles) patients at completion of chemotherapy. p values as compared with controls; horizontal lines are mean BMD values.

−1.38 to −0.19; $p < 0.01$) were significantly decreased compared with controls (table 3; fig 3). Lumbar BMD was significantly decreased in girls, as was femoral BMD in both boys and girls compared with controls (table 3). Among children with malignancies, no significant difference in BMD was seen between boys and girls, nor between ALL and other malignancy patients.

In the simultaneous regression analysis, no single chemotherapeutic agent showed an independent relation with the BMD values.

Days of hospitalisation correlated negatively with femoral areal and volumetric BMD ($r = -0.48$; $p = 0.01$ and $r = -0.58$; $p = 0.002$, respectively). Age at the time of the study correlated negatively with femoral volumetric BMD ($r = -0.39$; $p = 0.04$). Relative height correlated positively with femoral areal BMD ($r = 0.45$; $p = 0.02$). Durations of overall and corticosteroid treatments, BMI, age at diagnosis, and bone age at cessation of treatment did not correlate with the BMDs. No difference in BMD Z scores was found between pubertal and prepubertal patients at the time of our study.

Four patients (three girls) had primary hypogonadism according to a raised serum luteinising hormone concentration, and one girl had a compensated hypothyroidism at the time of completion of chemotherapy. Intact parathyroid hormone values were normal in 41 patients, high in four patients (two boys), and low in one boy.

Discussion

We have previously demonstrated decreased BMD in adolescent and adult long term survivors of childhood ALL.[11] Our present cross sectional study showed that children with ALL had significantly reduced lumbar volumetric and femoral areal and volumetric bone density already at the time of completion of chemotherapy. The children with other malignancies did not differ from healthy controls in their spine measurements. However, areal and volumetric femoral bone density were low also in this group of patients. The decline in apparent volumetric BMD indicated a real deficit in bone density. Decrease in only areal BMD in children might be a result of reduced bone size, but this was not the case in our study. An estimation of the volumetric BMD has not been performed in earlier studies in children with malignancies.[1–7]

The pathogenesis of osteopenia in childhood malignancies has not been clarified. It has been suggested that the disease itself or components of antineoplastic treatments can impair the development of bone mass and density.[1–13]

Treatment of childhood malignancies consists of various multiagent chemotherapy regimens.[15–22] They commonly include corticosteroids and methotrexate.[15–19 26] Osteoporosis is a well known complication of the prolonged use of corticosteroids. The major factor underlying corticosteroid induced osteoporosis is a decreased osteoblast activity and a decrease in the active life span of osteoblasts.[27–32] Corticosteroids have also been proposed to increase bone resorption as a consequence of secondary hyperparathyroidism resulting from a decrease in intestinal calcium absorption and an increase in urinary excretion of calcium.[33 34]

Methotrexate osteopathy has been reported in children with malignancies.[8–10] The mechanisms of the methotrexate effect on bone have been proposed to involve toxicity of high cellular concentrations of polyglutamate derivative resulting from the folate deficiency,[10] and the inhibition of osteoblast proliferation as shown in cultured human osteoblasts.[13] In addition, other anticancer agents, which are potent cytotoxins, might potentiate the adverse effects of corticosteroids and methotrexate on osteoblasts, impairing the development of bone mass and density.

We analysed the BMD effect of the cumulative doses of those antineoplastic agents that were used in both ALL and other malignancy groups: corticosteroids, methotrexate, cyclophosphamide, cytarabine, doxorubicin, and vincristine. In simultaneous regression

analysis, none of them showed an independent correlation with BMD and neither did the duration of corticosteroid treatment correlate with BMD. The role of individual drugs in inducing changes in bone metabolism in chronic diseases is difficult to assess because the diseases themselves and other treatment components might also affect bone development.[1 35]

Local skeletal radiation causing direct bone loss, gonadal irradiation impairing production of sex hormones, and cranial irradiation leading to growth hormone deficiency might all induce disorders in bone development.[6 12 36–40] In our study, 10 patients had received radiotherapy, which might have affected BMD. However, the large variation in the sites and in the doses of radiotherapy combined with a variety of administered antineoplastic agents did not allow us to study the specific effect of radiation on bone mineral density.

The finding that femoral BMD was reduced in both ALL and other malignancies but that lumbar BMD was reduced only in ALL patients is interesting. The spine, which is predominantly trabecular bone, has a much more rapid bone turnover than femoral neck, which on the other hand contains more cortical bone. These two anatomical sites can hence respond in different ways in various diseases and to specific treatments.[39] In previous studies, the bone loss induced by corticosteroids has been shown to be most rapid in the lumbar spine.[35] In our study, patients with ALL had received significantly higher doses of corticosteroids for a significantly longer duration compared with patients with other malignancies. Thus, the detected reduction in lumbar BMD in ALL, but not in the other malignancies, could partly be explained by a higher susceptibility of trabecular bone to corticosteroid treatment. In addition, it has been suggested that the leukaemic infiltration and expansion of the bone marrow spaces leading to destruction of spongiosa, as well as factors secreted by the leukaemic cells, such as osteoblast inhibiting factor and parathyroid hormone related peptide, might contribute to bone loss in ALL.[4]

The reduction of femoral BMD in ALL but also in the other malignancies indicated that femoral BMD might become impaired even during a shorter period of treatment, possibly as a consequence of disease and treatment related hospitalisation, leading to decreased physical activity, malnutrition, and reduced body mass, factors often seen in children with malignancies. This was partly corroborated by our finding of a negative correlation between femoral BMD and duration of hospitalisation.

Calcium malabsorption, alterations in vitamin D metabolism, growth hormone deficiency, and changes in insulin-like growth factors and their binding proteins are components that might also influence bone mineral density in children with malignant diseases.[35 36 40–42] Studies determining their role in bone development in childhood malignancies are underway in our unit.

In conclusion, osteopenia, osteoporosis, and pathological fractures have been observed in children with neoplasms.[1–11] In our study, we found reduced BMD in children with malignancies at the time of completion of chemotherapy. The reason for this reduction might be multifactorial, as discussed above.

The maximum increment rate of bone density occurs between the ages of 11 and 13 years in girls and 13 and 17 years in boys, and peak bone mass is achieved by around 20 years of age.[23 24 43] Most of the patients in our study had still to go through the period of maximum bone development. Thus, a follow up of BMD after completion of chemotherapy should facilitate the identification of those who might be left with impaired development of peak bone mass, and who would require specific therapeutic interventions to prevent any further decrease in their skeletal mass and to preserve their BMD.

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